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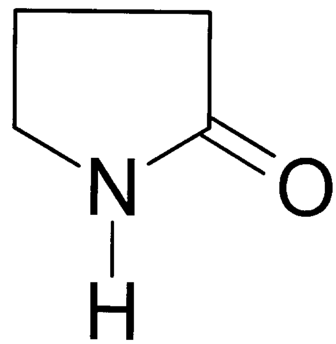
2-Pyrrolidone



CAS Number 616-45-5

U.S. EPA HPV Challenge Program Submission

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Submitted by:

2-Pyrrolidone Consortium

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Executive Overview

2-Pyrrolidone, CAS no. 616-45-5, is a cyclic amide prepared primarily from butyrolactone. It is a clear liquid with an unpleasant ammonia-like odor and a freezing point of 25° C. It has low volatility (boiling point 245 °C and vapor pressure of 0.013 hPa @ 25° C) and is miscible with water and most organic solvents. Its most extensive use is as a chemical intermediate but it is also used as a high-boiling solvent.

In the environment, based on physicochemical and experimental data, 2-Pyrrolidone will not bioaccumulate (Log $K_{o/w}$ = -0.71) and will distribute primarily to water where it will be subject to limited volatilization and rapid biodegradation. It is expected to react rapidly with atmospheric hydroxyl radicals with a half-life of about 11 hours. The toxicity of Propargyl alcohol to aquatic species is very low, with an LC_{50} for freshwater fish greater than 4600 mg/L and daphnia greater than 1000 mg/L.

The oral LD_{50} of 2-Pyrrolidone is very high with values of 8000 and greater than 5000 mg/kg being reported. Exposure of rats to saturated vapor for 8 hours did not produce any adverse effects and the dermal LD50 in rabbits is greater than 2000 mg/kg.

A modern subchronic drinking water study of 2-Pyrrolidone showed low repeated-dose toxicity with a 90-day NOAEL of 2400 ppm and a LOAEL of 7200 ppm in drinking water. The kidneys many have been affected but no target organs were identified by histopathological examination.

Adequate *in vitro* tests of genetic toxicity for 2-Pyrrolidone are available. A *Salmonella typhimurium* reverse mutation assay shows lack of mutagenic activity in the presence or absence of metabolic activation and a guideline cytogenetics study using human lymphocytes displayed a lack of genotoxicity activity in the presence or absence of metabolic activation.

Developmental toxicity has been investigated using an OECD 414 Guideline study. The results of this investigation conducted in rats by oral gavage at 0, 190, 600 or 1900 mg/kg-day indicate that 2-P affects the conceptus only at doses that exceed the maternally toxic level. The developmental NOAEL was found to be 600 mg/kg-day while the maternal NOAEL was 190 mg/kg-day.

The combination of the negative developmental toxicity study with a robust subchronic study in which specific damage to reproductive organs was not observed fulfills the current requirement for reproductive toxicity information.

It is concluded that the available information adequately fills all the data elements of the HPV. Although the available studies do not meet all the requirements of the current OECD guidelines in all cases, conduct of additional similar studies would not add significantly to our understanding of this material's hazard.

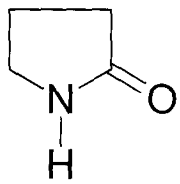
Testing Plan and Rationale

Testing Plan in Tabular Format

CAS Number 616-45-5 2-Pyrrolidone	Information Available?	OECD Study ?	GLP Study?	Supporting Information?	Estimation Method?	Acceptable?	Testing Recommended?
HPV Endpoint							
Physical Chemical							
Melting Point	Y	N	N	N	N	Y	N
Boiling Point	Y	N	N	N	N	Y	N
Vapor Pressure	Y	N	N	Y	N	Y	N
Partition Coefficient	Y	Y	N	Y	N	Y	N
Water Solubility	Y	N	N	Y	N	Y	N
Environmental & Fate							
Photo-Degradation	Y	N	N	N	Y	Y	N
Water Stability	Y	N	N	Y	Y	Y	N
Transport	Y	N	N	N	Y	Y	N
Biodegradation	Y	N	N	Y	N	Y	N
Ecotoxicity							
96-Hour Fish	Y	Y	N	Y	N	Y	N
48-Hour Invertebrate	Y	Y	N	Y	N	Y	N
72-Hour Algae	Y	Y	N	Y	N	Y	N
Toxicity							
Acute	Y	N	N	Y	N	Y	N
Repeated Dose	Y	Y	Y	N	N	Y	N
Genetic Toxicology *in vitro*	Y	N	Y	Y	N	Y	N
Genetic Toxicology *in vivo*	Y	N	Y	Y	N	Y	N
Reproductive	Y	N	N	Y	N	Y	N
Developmental	Y	Y	Y	Y	N	Y	N

Introduction

2-Pyrrolidone, CAS no. 616-45-5, is a cyclic amide prepared primarily from butyrolactone by a Reppe process (1). It is a clear liquid (above 25° C) with an unpleasant ammonia-like odor. It has low volatility and is miscible with water and most organic solvents. Its most extensive uses are as an intermediate in the manufacture of N-methylpyrrolidone, vinylpyrrolidone, polyvinylpyrrolidone and polypyrrolidone with over 95% of the 2-Pyrrolidone production going into vinylpyrrolidone (2). It is used as a high-boiling solvent in petroleum processing and acrylonitrile manufacture. It also finds application as a solvent for polymers, sorbitol, glycerol, iodine and sugars. Some is used as a plasticizer and coalescing agent for polymer emulsion coatings such as floor polishes. Another application is as humectant and co-solvent for digital printing inks. It's exceptional solvent properties make it very useful for the solubilization of complex organic material in water. Although it is an excellent solvent, the somewhat labile proton on the nitrogen limits its applications as an aprotic solvent. Its structure is shown below:
2-Pyrrolidone is also known as:



- 4-Aminobutyric acid lactam
- Gamma-aminobutyric lactam
- Gamma-aminobutyrolactam
- Butanoic acid, 4-amino-, lactam
- Butyrolactam
- Gamma-butyrolactam
- 2-Ketopyrrolidine
- 2-Oxopyrrolidine
- 2-Pyrol
- Apha-pyrrolidinone

The chemical and physical properties of 2-Pyrrolidone make it a unique solvent for certain applications and a useful chemical intermediate. There are several reports in the open literature of its utility as a skin-penetration enhancer with potential applications in transdermal drug delivery. This property and potential application seems to be a function of the physicochemical properties of this solvent and not a specific chemical reactive property. Another use in the pharmaceutical industry is in the production of pyrrolidone nootropics including piracetam (2).

Exposure in industrial applications is limited by process controls, protective equipment, a very low vapor pressure and excellent warning properties due to its objectionable odor. No occupational exposure level set by a governmental agency could be located for 2-Pyrrolidone. Use as a humectant and co-solvent in digital inks may result in a low-level of inhalation exposure by consumers limited by the very low quantities of inks used by digital printing devices.

Several physicochemical, fate and toxicity studies have been conducted on 2-Pyrrolidone. These studies are briefly reviewed in this testing rationale document, which also describes how these studies meet the SIDS (Screening Information Data Set) end-points of the United States Environmental Protection Agency (USEPA) High Production Volume Challenge (HPV) program. Robust summaries have been prepared for key studies; supporting studies are referenced in these summaries or given as shorter summaries using the IUCLID format. The available data set satisfactorily fulfills the data requirements for the EPA HPV Program. The majority of data elements are filled by high-reliability studies on 2-Pyrrolidone. Where direct data are not available or data are sparse, surrogates and estimations are used to fill the data element. This is encouraged by the U.S. EPA and other regulatory authorities to avoid unnecessary testing and animal usage.

Physicochemical Data

Physicochemical data for 2-Pyrrolidone are available from the literature and manufacturer's information.

Table 1: Physicochemical Properties of 2-Pyrrolidone	
Melting Point	25° C (3)
Boiling Point	245° C @ 1010 hPa (4)
Vapor Pressure	0.013 hPa @ 25° C (5)
Partition Coefficient	Log $K_{o/w}$ = -0.71 (6)
Water Solubility	Soluble in all proportions (7)

These properties indicate that above 25° C, 2-Pyrrolidone is slightly volatile liquid with high water solubility. The value of the partition coefficient suggests that 2-Pyrrolidone will partition preferentially into water and, therefore, has little potential for bioaccumulation.

Recommendation: No additional physicochemical studies are recommended. The available data fill the HPV required data elements.

Environmental Fate and Pathways

Biodegradation potential has been determined using a Zahn Wellens test. In this DOC removal test, DOC was 80% eliminated after 5 days of incubation (8). Although this only definitively shows "inherent biodegradability" the speed of removal and completeness (99% at 9 days) suggest that this material is easily biodegraded by non-adapted bacteria. Using BIOWIN 4.00, it can be estimated that 2-Pyrrolidone is readily biodegradable with quantitative estimates suggesting a high likelihood that it should be considered "readily biodegradable (9). Furthermore, the analog and surrogate compound, N-Methyl-2-pyrrolidone (NMP) has been demonstrated to be readily biodegradable in the MITI test (10). Comparative estimation using BIOWIN 4.00 suggests that NMP is likely to be slightly more resistant to aerobic biodegradation than 2-Pyrrolidone, although NMP still is indicated by BIOWIN to be readily biodegradable. The information that NMP biodegradation is correctly predicted as readily biodegradable by BIOWIN, and the strong structural similarity between the two compounds, validates the BIOWIN estimate for 2-Pyrrolidone.

Photodegradation was estimated using version 1.90 of the Atmospheric Oxidation Program for Microsoft Windows (AOPWIN) that estimates the rate constant for the atmospheric, gas-phase reaction between photochemically produced hydroxyl radicals and organic chemicals. The estimated rate constant is used to calculate atmospheric half-lives for organic compounds based upon average atmospheric concentrations of hydroxyl radical. The program produced a estimated rate constant of 11.9 E-12 cm^3/molecule-sec. Using the default atmospheric hydroxyl radical concentration in APOWIN and the estimated rate constant for reaction of 2-Pyrrolidone with hydroxyl radical, the estimated half-life of 2-Pyrrolidone vapor in air is approximately 10.75 hours (see accompanying robust summary).

Water stability has not been quantitatively determined for 2-Pyrrolidone. Quantitative stability determinations (e.g. OECD 111) are considered unnecessary for compounds containing only non-hydrolysable groups, as the SIDS manual states that consideration should be given to using an estimation method. There is no evidence available that 2-Pyrrolidone is unstable in water, although it has a potentially hydrolysable amide group, amides are considered resistant to hydrolysis at environmental pH values and require strong base or acid to accomplish hydrolysis. Vollhardt states: "Amides are the least reactive of the carboxylic derivatives, mainly because of the extra resonance capacity of the nitrogen lone electron pair. As a consequence, their nucleophilic addition-eliminations require relatively harsh conditions. For example, hydrolysis occurs only on prolonged heating in strongly acidic or basic water"(11). The HYDOWIN program recognized this when an estimate of hydrolysis was attempted. The HYDROWIN output was that the compound had an amide group and the hydrolysis rate was extremely slow, the HYDROWIN program estimated the half-life in water greater than one year (12). This estimated is confirmed by the review of Harris, who notes that the mean hydrolytic half-life for a series of amides is in the range of 300 years (13). In addition, this is a cyclic amide in a 5-membered ring, which is generally the ring size showing the least strain and, hence making ring opening a less favored occurrence increasing resistance to hydrolysis.

Theoretical Distribution (Fugacity) of 2-Pyrrolidone in the environment was estimated using the MacKay EQC level III model with standard defaults in EPIWIN v 3.05 but using the measured vapor pressure of 0.013 hPa and the measured log $K_{o/w}$ (14). The results for distribution using a model calculated $K_{o/c}$ (adsorption coefficient based on organic carbon content) of 0.0799 and equal initial distribution to air, water and soil are:

- Air 0.4 %
- Water 46.5 %
- Soil 53.0 %
- Sediment 0.08 %

Recommendation: No additional fate studies are recommended. The available data fill the HPV required elements.

Ecotoxicity

A recent GLP guideline (OECD 203) study of acute fish toxicity using measured concentrations of 2-Pyrrolidone is available demonstrating low hazard to zebra fish after 96 hours of exposure. The test material stability in the dilution water with fish was very good over the 96-hour period. Daphnia studies indicate an EC_{50} greater than 1000 mg/L in one test, greater than 500 mg/L in another guideline-like study and a report of an EC_{50} values less than 20 mg/L. Although experimental data give differing results, the weight of evidence indicates a low aquatic hazard. Other invertebrates, specifically, flatworms and snails, showed no effects in limit tests at 112 mg/L. Algae growth inhibition, according to a guideline study, has an EC_{50} of about 84 mg/L after 96-hours. These values with references are shown in the table. ECOSAR estimates, using the neutral organic model, are also given in the table below for comparison. In addition, a bacterial growth inhibition test using *Pseudomonas putida* resulted in an EC_{50} of 9368 mg/L, with lower concentrations showing stimulation of bacterial growth (15).

Table 2: Comparative Aquatic Toxicity of 2-Pyrrolidone

	Reported Values	ECOSAR Prediction
Fish, 96 hour LC_{50}	> 4600 mg/L (16)	9566 mg/L*
Daphnia, 48 hour EC_{50}	> 500 mg/L (17) > 1000 mg/L (18) = 13.2 mg/L (19)	8733 mg/L*
Algae, 96 hour EC_{50}	= 84 mg/L (20)	4777 mg/L*

* Estimated using ECOSAR (21)

Unvalidated, but multiple, study results reported in IUCLID 2000 (22) indicate that the analog 1–methyl–2–pyrrolidone has low acute toxicity to fish, invertebrates and algae (short-term LC_{50} or EC_{50} values >500 mg/L). This lends support to the higher values for the LC_{50} and EC_{50} values of 2-Pyrrolidone that have been reported. The reason some investigations have found higher degrees of toxicity is unknown but a reasonable speculation would be that the samples tested were contaminated with more toxic agents. For example, it is known that γ-Butyrolactone which is one of the primary starting materials for 2-Pyrrolidone is more toxic to fish and daphnids. Likewise, aliphatic amines, which are potential side products from 2-Pyrrolidone manufacture, typically have LC and EC_{50} values in a range where contamination of a sample might result in a low EC_{50}.

Recommendation: No additional ecotoxicity studies are recommended. The available data fill the HPV required endpoints. Although experimental data give differing results, the weight of evidence indicates low aquatic hazard. This information coupled with the information that 2-Pyrrolidone is biodegraded easily in the environment and has a low log $K_{o/w}$ constant reduce the concern level for potential environmental hazard. Conduct of additional studies would not add significantly to our understanding of this material's toxicity and it is recommended that no additional ecotoxicity studies be conducted.

Health Effects

Acute Toxicity

Oral Exposure

Multiple determinations of the oral LD_{50} of 2-Pyrrolidone have been reported (23) and the studies universally indicate a low order of acute oral toxicity for this material. Two robust summaries have been prepared from BASF study reports. One indicted an LD_{50} of approximately 8000 mg/kg-bw (24) and the other was a limit test at 5000 mg/kg-bw in which there were no mortalities or adverse clinical signs except for transient loss in male body weights (25).

Inhalation Exposure

It has been reported that there were no deaths when rats were exposed to saturated vapor of 2-Pyrrolidone for 8 hours (26). The actual concentration was not measured but based on the vapor pressure at 30°C the vapor concentration is calculated to be in the range of 15-20 ppm.

Dermal Exposure

A guideline (OECD 402) limit study has indicated that the dermal LD_{50} of 2-Pyrrolidone in rabbits is greater than 2000 mg/kg-bw (27).

Recommendation: No additional acute toxicity studies are recommended. The available data fill the HPV required endpoints for acute toxicity. Although the available studies do not meet the requirements of the current OECD guidelines in all cases, the weight of evidence shows that the oral and dermal toxicity is very low. Likewise, the limited study of acute saturated vapor inhalation provides important and scientifically defensible information about vapor toxicity. Conduct of additional studies would not add significantly to our understanding of this material's toxicity and it is recommended that no additional acute toxicity studies be conducted.

Repeat Dose Toxicity

Oral Exposure

A guideline-glp 90-day study in rats has been conducted. In this study, 2-Pyrrolidone was administered to groups of 10 male and 10 female Wistar rats at doses of 0; 600; 2,400; 7,200 and 15,000 ppm in the drinking water over a period of 3 months (28). No animals died nor were any adverse clinical signs of exposure reported. In the high-dose group, food and water consumption, and body-weight gain were reduced for males and females; kidney weights for males and females were increased; other minor treatment related effects were in prolonged prothrombin times and decreased serum protein, globulins, creatinine and triglycerides. At 7,200 ppm, water consumption was reduced in rats of each sex; food consumption and body weight gain were reduced only for females; kidney weights for males were increased; other minor treatment related effects were in and decreased serum total protein for females and decreased creatinine in both sexes. The 2,400 ppm dose was a NOAEL. Gross pathology, organ weight determination and full histopathology were conducted on all animals. No treatment-related histopathologic effects were observed.

Recommendation: No additional repeated-dose studies are recommended. The available data conducted by OECD Guidelines and under GLP fill the HPV required endpoint for repeated-dose toxicity.

Genetic Toxicity

The SIDS/HPV requirement for genetic toxicity screening is for two end-points: generally one sensitive to point mutation and one sensitive to chromosomal aberrations. In the case of this material, adequate tests have been conducted that cover both of these endpoints.

Genetic Toxicology in vitro

Adequate *in vitro* tests of genetic toxicity for 2-Pyrrolidone are available. A *Salmonella typhimurium* reverse mutation assay shows lack of mutagenic activity in the presence or absence of metabolic activation (29). Likewise, a guideline cytogenetics study using human lymphocytes displayed a lack of genotoxicity activity in the presence or absence of metabolic activation (30).

Genetic Toxicology in vivo

Mammalian genotoxicity was assessed *in vivo* using the Mouse Micronucleus Test. In this OECD-Guideline-474 study, a single i.p. dose of 2-Pyrrolidone did not result in an increase in normochromatic erythrocytes containing micronuclei. It was concluded that the test material did not show genotoxic activity in this system (31).

Recommendation: The SIDS requirement for genetic testing has been met as assays sensitive to both point mutation and to clastogenic effects have been conducted using acceptable protocols. No additional genotoxicity testing is recommended.

Reproductive Toxicity

The combination of the negative developmental toxicity study (32) with a robust subchronic study (28) showing that, even at systemically toxic doses, there is no specific damage to reproductive organs of males or females, fulfills the current requirement for reproductive toxicity information.

Recommendation: No additional reproductive testing is recommended, as the available data are sufficient to assess the reproductive toxicity of this material.

Developmental Toxicity

A modern OECD 414 Guideline study has been conducted with 2-Pyrrolidone. The results of this investigation conducted in rats by oral gavage at 0, 190, 600 or 1900 mg/kg-day indicate that 2-Pyrrolidone is embryotoxic at doses that exceed the maternally toxic level. The developmental NOAEL was found to be 600 mg/kg-day while the maternal NOAEL was 190 mg/kg-day. Even at the maximum dose level of 1900 mg/kg-day the developmental toxicity was not severe (32). This result is supported by an older single-dose-level teratology study at about 1900 mg/kg-day in the same strain of rat by oral gavage. In this study, 25 presumed-pregnant dams were treated from day 6 to 15 of gestation. Fetuses were delivered by Caesarean section on GD-20 and examined for external, visceral and skeletal abnormalities. No differences were reported between the control and treated animals (33). A mouse teratology study using i.p. injection has also been conducted. Some degree of developmental toxicity was reported in this study but the effect was considered due to stress on the animals from the i.p. injections (34). The proposed explanation is consistent with mouse physiology; moreover, the route of exposure is inappropriate in a consideration of hazard or risk assessment.

Taken together, the weight of evidence from these developmental toxicity studies indicate a low developmental toxicity hazard for 2-Pyrrolidone.

Recommendation: No additional developmental toxicity testing is required as the available data are sufficient to assess the developmental toxicity of this material.

Conclusions

With regard to the parameters specified in the EPA HPV Challenge program, it is concluded that the available information fills all of the requirements for physicochemical parameters, fate information, aquatic toxicity and mammalian toxicity. Although the available studies do not meet all the requirements of the current OECD guidelines in all cases, taken together the information provided a reliable hazard assessment. Conduct of additional studies would not add significantly to our understanding of this material's toxicity.

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